PODIUM SESSION III: MODELING METHODS II

MO5

THE USE OF SURVIVAL ANALYSES FOR COST-EFFECTIVENESS MODELS: AN EVALUATION OF METHODS USED IN NICE APPRAISALS

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BACKGROUND AND OBJECTIVE: In the area of oncology and cardiovascular disease, treatments often effect overall survival, progression free survival and other time-to-event outcomes. For such treatments, the evaluation of cost-effectiveness often implies an extrapolation of trial results to periods beyond the trial length. The choice of extrapolation function may have a substantial impact on the mean survival: in some of our projects, the mean survival using the log-normal and log-logistic distribution was more than 1.5 times larger than the mean survival using the weibull distribution. This triggered us to perform an evaluation of methods used for extrapolation in NICE submissions, in order to know which methods were accepted. **METHODS**: CEAs published between 2004 and 2008 by the NICE Technology Appraisal programme, which included failure-time outcome(s), were systematically reviewed with respect to curve fitting procedures used for extrapolation. **RESULTS**: In the HTA reports, exponential, weibull, log-logistic or log-normal curves were fitted. The distribution was chosen based on face-value, by comparing it with the Kaplan Meier Curve. The quality of the graphical methods is limited, especially because the three curves often have a comparable fit. In the reports, the proportional hazard assumption was used to compare the treatment arm with the comparator arm, often without assessing the validity of the assumption. **CONCLUSION:** The choice of methods used to extrapolate survival curves in HTA reports has been inadequately justified, and has under-estimated uncertainty. In our opinion, researchers should: assess the validity of proportional hazards and use different methodology when the assumption is violated; evaluate goodness-of-fit more appropriately. Consider using a generalized distribution, for which the weibull, log-logistic and log-normal are special cases.

MO6

MODELLING COST EFFECTIVENESS OF DRUGS THAT DELAY DISABILITY PROGRESSION IN MULTIPLE SCLEROSIS: A NOVEL APPROACH

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OBJECTIVES: To describe a novel approach to modelling the outcomes, costs and cost-effectiveness of disease-modifying drugs (DMDs) that delay disability progression in multiple sclerosis (MS). **METHODS:** MS natural history was modelled using Kaplan-Meier survival distribution estimates for 18 expanded disability status scale (EDSS) endpoints (1.0 to 9.5) in each of 40 years since MS onset (YSO). NH estimates were based on 1,607 individuals with 6,993 clinic visits to the Dalhousie MS Research Unit (DMSRU), Nova Scotia, Canada, over 25 years (1979–2004). DMD effectiveness was measured as the relative increase in YSO between EDSS endpoints and was derived from DMSRU data and the literature. DMDs were modelled as a class and were not differentiated by specific drug. To measure health outcomes as quality adjusted life years (QALYs), EDSS disability scores were converted to HUI3 scores. DMD treatment gains were estimated by the difference in QALYs experienced by the NH and DMD cohorts over 40 YSO. Annual DMD costs, net of foregone EDSS-specific health care costs, were derived from person-level DMSRU data linked to Nova Scotia health services utilization data. Cost-effectiveness of DMDs was measured as cost/QALY gained. Costs and QALYs were discounted by 3% annually. Key scenario parameters include DMD treatment eligibility, YSO at DMD start, DMD switching and stopping, initial and final MS classification, analysis horizon and discount rate. **RESULTS:** The results reflect the increased time to EDSS endpoints with DMD therapy and demonstrate the feasibility of using person-level data and a Kaplan-Meier approach to model costs and outcomes in MS with and without DMDs. **CONCLUSIONS:** This novel approach incorporates much more detailed MS natural history, DMD effectiveness and cost data than earlier models, allowing a more precise representation of the clinical and economic impact of MS DMD treatment programs.

MO7

EVALUATION OF A BAYESIAN COMPREHENSIVE DECISION-ANALYTICAL MODELLING FRAMEWORK IN CHRONIC HEPATITIS C

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OBJECTIVES: A standard approach to economic evaluation is to conduct a meta-analysis to subsequently inform a decision-analytical model. An innovative approach is to implement the meta-analysis and model evaluation simultaneously, in a Bayesian framework. These approaches were compared in two Markov models for chronic hepatitis C (CHC), where transition probabilities were not directly observable. **METHODS:** We updated a published meta-analysis on progression rates in CHC. Included studies provided distributions of patients by disease severity level, for different durations of infection. Two structures were considered to model disease progression: one with three states ("mild CHC", "moderate CHC", cirrhosis), another more complex with five states. The following methodological approaches were compared: 1) the "standard" approach involving successively maximum-likelihood estimation of progression rates for each study, random-effect meta-analysis of resulting estimates, Markov model evaluation and probabilistic sensitivity analysis, and 2) an integrated approach with estimation of progression rates and model evaluation in one Monte Carlo Markov Chain simulation procedure. The impact of methodological approach and model structure on predicted numbers of cirrhotic patients and total costs from NHS perspective at 20 years was analysed. **RESULTS:** The five-state model predicted the following proportions of cirrhotic patients: 39.6% (standard deviation: 0.075) and 50.2% (0.019) with approaches (1) and (2). The 3-state structure provided lower estimates: 19.7% (0.0911) and 22.3% (0.011) with approaches (1) and (2). For the 5-state model, predicted costs per patient were £7,120 (934) and £8,000 (856) with each approach respectively. **CONCLUSIONS:** The comprehensive modelling approach lead to higher mean estimates with lower variability than the standard approach. The simpler three-state structure seems to underestimate the burden of disease. The latter finding may have relevance for modelling progressive diseases more generally.

MO8

MARGINAL STRUCTURAL MODELS FOR COMPARING THE EFFECTIVENESS OF MULTIPLE TREATMENTS IN OBSERVATIONAL STUDIES

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OBJECTIVES: Longitudinal studies comparing treatments in real-world practice settings may be threatened by bias due to time-dependent confounding from factors predicted by the treatment history. While standard statistical methods may fail to control this type of confounding, Marginal Structural Models (MSM) can be a better alternative. The objective of this paper is to illustrate the fitting of a MSM to compare more than two treatments. **METHODS:** MSMs apply inverse probabilities of treatment weights (IPTW), which can be derived from multinomial logistic regression models for predicting probability of treatments and censoring in a particular time period. IPTW are then used in a Generalizing Estimating Equation (GEE) to estimate the causal effect of treatment on outcome. In this study, data from a national cohort of patients diagnosed with Chronic Heart Failure (CHF) from October 1, 1996(FY 1997) to September 30, 2002 (FY 2002) in the VA were used (n = 19,569). The treatment groups were defined based on the time-varying utilization of different angiotensin receptor blockers (ARB): candesartan, irbesartan, losartan, telmisartan, valsartan or no ARB each month starting from their first prescription fill in FY 2001 and FY 2002. The outcome assessed was mortality during the same time period. In addition to adjusting for sociodemographic factors, comorbidities, comedications hospitalization was the time-varying confounder considered. **RESULTS:** Hospitalization changed the predicted probabilities of treatment over time. In adjusted models, compared to Losartan, all the ARBs had similar effectiveness in reducing mortality except for telmisartan, which was associated with increased risk (OR 1.77, 95% CI = 1.01–3.09). The no ARB group had the highest risk of mortality (OR 2.76, 95% CI = 2.33–3.27). **CONCLUSIONS:** Marginal structural models can be used efficiently to compare more than two treatments in longitudinal observational studies where time dependent confounding affected by previous treatment may pose a serious threat to internal validity.

PODIUM SESSION III: PRO/QOL METHODS – CROSS CULTURAL ADAPTATION

PR1

A LATENT GENERAL GROWTH MIXTURE MODEL FOR HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH PARKINSON DISEASE ACROSS 36 MONTH

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OBJECTIVES: To analyze the change in health-related quality-of-life (HrQoL) in a cohort of patients with Parkinson's disease(PD) and to identify different groups of HrQol patterns across 36 months. **METHODS:** Clinical parameters(Unified PD rating scale (UPDRS), Beck depression inventory(BDI)) and HrQoL data(EuroQol) were assessed in a cohort of 145 PD assessed at baseline, 3, 6, 12, 18, and 36 months. 31 patients were lost to follow-up. EQ-5D data were analyzed with a piecewise growth mixture model(gender, UPDRS and BDI adjusted model parameters) to identify distinct HrQoL trajectory groups. **RESULTS:** The average overall EQ-5D was .58 at baseline(BL) followed by a moderate decline(dec) of .12 across 36 months. However, we found a remarkable heterogeneity between patient's trajectories. A Latent Growth Model was applied resulting in a four-class model of distinct patterns in the EQ-5D course. Class one included patients with a moderate level of clinical parameter severity(UPDRS, BDI) at baseline and an almost constant high EQ-5D index score(BL: .80, dec: .07) during 36 months. Class two reflected the average HrQoL course of the whole PD population with a minimal decline during 36 months(EQ5D BL .56; dec .01). The third group consisted mainly(88%) of patients who passed away during the observation time and therefore had a large HrQoL decline(EQ-5D BL: .60; dec .4). Class four was characterized by a low level of EQ-5D at baseline(.36) and a significant subsequent decline(.16). **CONCLUSIONS:** Present findings provide a more elaborate understanding of the variability of HrQoL reduction in PD over time. The classification of different HrQol subgroups may help to understand PD patients' responsiveness to the natural history of disease. Future research is needed to enable the identification of certain responder subgroups in terms of HrQoL upon different treatment regimens. This may also allow a more targeted and systematic PD therapy.